OFFICES OF REVIEW MANAGEMENT AND PHARMACEUTICAL SCIENCES

INDs: Screening INDs

CONTENTS

PURPOSE

- This MAPP describes procedures for the review of multiple active moieties or formulations under a single investigative new drug application (IND) called a *screening IND.*

BACKGROUND

- In general, CDER policy has been to encourage separate INDs for different molecules and dosage forms. However, in the early phase of drug development, before the developmental path is clear, exploratory studies may be conducted on a number of closely related drugs to choose the preferred compound or formulation. These studies may be best and most efficiently conducted under a single IND, referred to as a *screening IND.* This MAPP outlines procedures for determining (1) when a single IND is sufficient and appropriate, and (2) when an additional IND should be opened.

REFERENCES

- Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (Modernization Act), November 21, 1997. *http://www.fda.gov/cder/guidance/105-115.htm#SEC. 111*

- FDA guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology Derived Products* (November 1995).

- Memo, *Guideline for the Establishment of a New IND, NDA, or Supplemental NDA for New Indications and Dosage Forms,* from the Acting Associate Director for New Drug Evaluation, January 9, 1975.

- ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (July 1997).

- FDA guidance for industry on *Single Dose Acute Toxicity Testing for Pharmaceuticals* (August 1996).

DEFINITIONS

- **COMIS:** Centerwide Oracle-based Management Information System.

- **CMC:** Chemistry, manufacturing, and controls.

- **Early Development Studies:** Single-dose or multiple-dose pharmacokinetic (PK), pharmacodynamic (PD), or biopharmaceutic studies. They can involve a single active ingredient or dosage form, multiple salts, esters, or even a group of closely related active moieties.

- **Screening IND:** A single IND submitted for the sole purpose of comparing the properties of closely related active moieties to screen for the preferred compounds or formulations. These compounds or formulations can then become the subject of additional clinical development, each under a separate IND.

POLICY

- Early exploratory clinical trials may be conducted under a single IND (screening IND) that generally uses similar protocols of multiple, closely

- The screening IND is intended for early exploratory studies only. When the early exploratory trials are completed, the screening IND should be withdrawn. A new IND should be opened when follow-up studies are planned for one or more of the moieties or when additional, closely related chemical moieties are to be clinically tested.

- The CMC and nonclinical pharmacology and toxicology data for each active moiety in a screening IND should be in accord with appropriate FDA guidances.

- Screening INDs generally apply to short-term Phase 1 tolerance, pharmacokinetic, pharmacodynamic, and early pilot efficacy studies.

PROCEDURES

- **Screening IND Assignment:** Assignment of a screening IND to a review division should follow the usual procedures based on therapeutic intent. If this information is not available, assignment of the review responsibility should be based on pharmacological class.

- **Screening IND Properties:** Screening INDs are appropriate when single-dose or short-term, repeat-dose clinical trials (#3 days of dosing) are proposed using multiple, closely related compounds. The compounds include different salts or esters and active moieties that are slightly different chemically, but appear to be similar in pharmacodynamic properties. The proposed studies could be a single trial with multiple compounds or similar trials involving only one compound (e.g., several PK studies, one for each compound). The number of compounds tested should usually be #5. Normally, the intent of the study is to compare the properties of the closely related active moieties to screen for further development. The IND should be opened with all of the test active moieties defined and with adequate nonclinical and CMC data to support each moiety. The usual responsibilities for a Phase 1 study apply. In addition, the screening IND covers only the protocols in the initial

submission.

- **Screening IND Withdrawal:** When the proposed clinical trials with multiple, closely related active moieties are completed, the screening IND should be withdrawn. If subsequent clinical studies are planned with any of the test moieties from a screening IND, a new IND should be opened to investigate each active moiety (a single IND can be used for different formulations or different salts or esters of the same active moiety).

- **Follow-up INDs:** A new screening IND should be submitted if additional active moieties closely related to those present in the original screening IND are proposed for clinical testing. A new protocol for testing additional active moieties should not be submitted to an existing screening IND.

RESPONSIBILITIES

Central Document Room Staff:

- When an IND covers more than one active moiety, the staff enters all drug names (including code names) into COMIS in alphanumeric order.

Review Division Project Management Staff (Project Manager):

- Confirms that a cover letter is submitted with the IND stating the intent to investigate several closely related active moieties.

- Confirms that there is a single protocol design or closely related designs.

- Notifies sponsor that the screening IND will need to be withdrawn and that a new IND will have to be submitted when development of a drug product advances past the screening IND clinical protocols. Explains to the sponsor that any subsequent INDs should include:

  (A) The IND number of all other INDs for the same active moiety
  (B) The name of the original review division for the screening IND
  (C) The status of any other related INDs

- Explains to the sponsor that the new INDs need not include information already submitted to any other IND and that the screening IND can be cross-referenced.

- Ensures that all drug names (including code names) are entered into COMIS when multiple active moieties are studied under a single IND.

All Review Team Members:

- Prior to the 30-day safety review, ensure that the protocols have addressed all the known risks associated with each of the active moieties proposed for screening in the clinical trial.

- Examine IND amendments to determine whether additional INDs should be opened based on the principles stated above. Inform Project Manager of amendments that need new INDs.

- Formally or informally consult with reviewers in other divisions whenever appropriate. May consult with the reviewers before an IND is submitted, when there is a new pending IND, or at any time during the development process. Keep their counterparts in other divisions informed of new information received about the INDs for closely related active moieties.

Chemistry and Pharmacology Team Leaders:

- Confirm that adequate CMC and nonclinical pharmacology/toxicology information has been submitted to ensure reasonable safety of the subjects in the screening IND.

Medical Officer and Team Leader:

- Determine whether the clinical protocol design addresses the intent of the study.

- Ensure that study subjects are adequately protected by the study design and monitoring plans.

Biopharmaceutics Reviewer and Team Leader:

- For studies designed to assess pharmacokinetic parameters, evaluate whether the pharmacokinetic parameters to be measured can be determined with the study design.

EFFECTIVE DATE

This MAPP is effective upon date of publication.